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1	32	(Thomas near Gardella.in.) or (henry near kronenberg.in.) or (John near Potts.in.) or (harald near Juppner.in.)	USPAT; US-PGPUB	2003/09/30 10:26
2	15	((Thomas near Gardella.in.) or (henry near kronenberg.in.) or (John near Potts.in.) or (harald near Juppner.in.)) and parathyroid adj1 hormone	USPAT; US-PGPUB	2003/09/30 10:28
3	3	parathyroid adj1 hormone same linker?	USPAT; US-PGPUB	2003/09/30 10:30
4	686	parathyroid adj1 hormone and linker?	USPAT; US-PGPUB	2003/09/30 10:46
6	10	PTH same linker	USPAT; US-PGPUB	2003/09/30 10:47

	U	1	Document ID	Issue Date	Pages	Title	Current OR
1	<input type="checkbox"/>	<input type="checkbox"/>	US 20030039654 A1	20030227	48	Modulators of receptors for parathyroid hormone and parathyroid hormone-related protein	424/178.1
2	<input type="checkbox"/>	<input type="checkbox"/>	US 20030100000 A1	20030529	43	Methods and compositions for reverse translation	435/6
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030143258 A1	20030731	41	Bone graft	424/426
4	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030166833 A1	20030904	23	Growth factor modified protein matrices for tissue engineering	530/300
5	<input type="checkbox"/>	<input type="checkbox"/>	US 5534440 A	19960709	21	Compounds and methods for sequencing amino acids	436/89
6	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5543264 A	19960806	68	Co-factor activated recombinant adenovirus proteinases	435/219
7	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5885821 A	19990323	54	Process for production of secretory Kex2 derivatives	435/224
8	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5935840 A	19990810	66	Activated recombinant adenovirus proteinases	435/252.3
9	<input type="checkbox"/>	<input type="checkbox"/>	US 6051399 A	20000418	49	Production of C-terminal amidated peptides from recombinant protein constructs	435/69.1
10	<input type="checkbox"/>	<input type="checkbox"/>	US 6136564 A	20001024	15	Process for the production of peptides by way of streptavidin fusion proteins	435/69.4

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1	514/102; 514/12		Kostenuik, Paul et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	435/7.1; 530/322		Martin, Mark T.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	514/12; 514/59; 514/60		Knaack, David et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	435/193; 435/395		Lutolf, Matthias et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	530/334; 530/335; 530/337; 530/412; 530/417		Aebersold, Rudolf H. et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	435/252.33 ; 435/320.1; 435/69.1; 435/69.7; 536/23.2		Anderson, Carl W. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	435/254.2; 536/23.2		Magota, Koji et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	435/252.33 ; 435/320.1; 435/69.1; 536/23.2; 536/23.4		Anderson, Carl W. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	435/68.1; 435/69.4; 435/69.7; 435/69.8; 530/308; 530/324; 530/345; 536/23.4		Stout, Jay S. et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	435/252.3; 435/254.2; 435/320.1; 530/399; 530/402; 536/23.4		Kopetzki, Erhard	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030144209 A1	20030731	26	Amino -terminal modified parathyroid hormone (PTH) analogs	514/12
2	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030153041 A1	20030814		Parathyroid hormone receptor and DNA encoding same	435/69.1
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030162256 A1	20030828	53	PTH1R and PTH3R receptors, methods and uses thereof	435/69.1
4	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20030166838 A1	20030904		Bioactive peptides and peptide derivatives of parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP)	530/327
5	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5171670 A	19921215		Recombinant DNA method for production of parathyroid hormone	435/68.1
6	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5494806 A	19960227		DNA and vectors encoding the parathyroid hormone receptor, transformed cells, and recombinant production of PTHR proteins and peptides	435/69.1
7	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5840853 A	19981124		Parathyroid hormone receptor and DNA encoding same	530/387.1
8	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5886148 A	19990323		Parathyroid hormone receptor	530/350
9	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6147186 A	20001114		Parathyroid hormone-related peptide analog	530/324

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1	530/324		Bringhurst, F. Richard et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	435/320.1; 435/325; 530/350; 536/23.5		Segre, Gino V. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	435/320.1; 435/325; 514/12; 530/350; 536/23.5		Juppner, Harald et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	530/328; 530/329		Gardella, Thomas J. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	435/252.3; 435/252.33 ; 435/254.2; 435/320.1; 435/69.4; 435/69.7; 530/350; 530/399		Kronenberg, Henry M. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	435/252.3; 435/254.2; 435/365; 530/324; 530/326; 530/350; 536/23.5; 536/24.31		Segre, Gino V. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	424/130.1; 424/139.1; 424/141.1; 424/143.1; 530/387.9; 530/388.1; 530/388.22		Segre, Gino V. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	435/252.3; 435/320.1; 435/325; 435/69.1; 435/7.1; 530/300		Segre, Gino V. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	530/300		Gardella, Thomas J. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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10	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6362163 B1	20020326	24	Parathyroid hormone-related peptide analogs	514/12
11	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6417333 B1	20020709		Modified human parathyroid hormone	530/351
12	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6495662 B1	20021217		Bioactive peptides and peptide derivatives of parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP)	530/300
13	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6537965 B1	20030325		Amino-terminal modified parathyroid hormone (PTH) analogs	514/2
14	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6541220 B1	20030401		Nucleic acid encoding PTH1R receptor	435/69.1
15	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US RE37919 E	20021203		Recombinant DNA method for production of parathyroid hormone	435/68.1

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11	424/85.1; 530/324; 530/326; 530/350		Bringhurst, F. Richard et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12			Gardella, Thomas J. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	424/1.11; 424/198.1; 424/85.1; 514/12; 514/13; 530/300; 530/324; 530/326; 530/388.22 ; 530/399		Bringhurst, F. Richard et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	435/252.3; 435/254.11 ; 435/320.1; 435/325; 435/471; 435/71.1; 435/71.2; 530/350; 536/23.5; 536/24.3; 536/24.31		Juppner, Harald et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	435/252.3; 435/252.33 ; 435/255.1; 435/320.1; 435/325; 435/69.4; 435/69.7; 530/350; 530/399; 536/23.1; 536/23.4; 536/23.51		Kronenberg, Henry M. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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US 20030039654A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0039654 A1**
(43) **Pub. Date: Feb. 27, 2003**
Kostenuik et al.(54) **MODULATORS OF RECEPTORS FOR
PARATHYROID HORMONE AND
PARATHYROID HORMONE-RELATED
PROTEIN**(75) **Inventors: Paul Kostenuik, Newbury Park, CA
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THOUSAND OAKS, CA 91320-1799 (US)**(73) **Assignee: Amgen Inc.**(21) **Appl. No.: 09/843,221**(22) **Filed: Apr. 26, 2001****Related U.S. Application Data**(60) **Provisional application No. 60/266,673, filed on Feb.
6, 2001. Provisional application No. 60/214,860, filed
on Jun. 28, 2000. Provisional application No. 60/200,
053, filed on Apr. 27, 2000.****Publication Classification**(51) **Int. Cl.⁷ A61K 39/395; A61K 31/66;
A61K 38/17**(52) **U.S. Cl. 424/178.1; 514/12; 514/102**(57) **ABSTRACT**

The present invention concerns therapeutic agents that modulate the activity of PTH and PTHrP. In accordance with the present invention, modulators of PTH and PTHrP comprise:

- (a) a PTH/PTHrP modulating domain; and
- (b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred; wherein the vehicle is covalently attached to the C-terminus of the PTH/PTHrP modulating domain. The vehicle and the PTH/PTHrP modulating domain may be linked through the N- or C-terminus of the PTH/PTHrP modulating domain, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Preferred PTH/PTHrP modulating domains comprise the PTH and PTHrP-derived amino acid sequences described hereinafter. Other PTH/PTHrP modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein. Such peptides typically will be modulators of both PTH activity and PTHrP activity, although such techniques can be used to generate peptide sequences that serve as selective modulators (e.g., agonists of PTH activity but not PTHrP activity).